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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY

(51) International Patent Classification ⁷ : A61K 38/17, 39/395 // C07K 16/28, 14/705	A2	(11) International Publication Number: WO 00/15247 (43) International Publication Date: 23 March 2000 (23.03.00)
(21) International Application Number: PCT/US99/21170 (22) International Filing Date: 13 September 1999 (13.09.99) (30) Priority Data: 60/100,182 14 September 1998 (14.09.98) US (71) Applicant (for all designated States except US): BIOGEN, INC. [US/US]; 14 Cambridge Center, Cambridge, MA 02142 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MUNDY, Gregory, R. [US/US]; 3719 Morgan's Creek, San Antonio, TX 78230 (US). YONEDA, Toshiyuki [JP/US]; 3530 Hunters Sound, San Antonio, TX 78230 (US). (74) Agent: KAPLAN, Warren, A.; Biogen, Inc., 14 Cambridge Center, Cambridge, MA 02142 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS (57) Abstract Antagonists of alpha4 integrin/alpha4 integrin ligand adhesion, which inhibit the biological effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing bone destruction associated with multiple myeloma. The homing of multiple myeloma cells to bone marrow and their alpha4 integrin-dependent release of bone-resorbing factors, resulting in bone destruction in patients with multiple myeloma, is inhibited.		

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(54) Title: METHODS OF TREATING MULTIPLE MYELOMA AND MYELOMA-INDUCED BONE RESORPTION USING INTEGRIN ANTAGONISTS (57) Abstract Antagonists of alpha4 integrin/alpha4 integrin ligand adhesion, which inhibit the biological effects of such adhesion are described and methods for their use are detailed. Such antagonists are useful in suppressing bone destruction associated with multiple myeloma. The homing of multiple myeloma cells to bone marrow and their alpha4 integrin-dependent release of bone-resorbing factors, resulting in bone destruction in patients with multiple myeloma, is inhibited.		

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 99/21170	
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K38/17 A61K39/395 //C07K16/28,C07K14/705	
According to International Patent Classification (IPC) or to both national classification and IPC	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K	
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched	
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)	
C. DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages
X	MASELLIS-SMITH A ET AL: "Adhesion of multiple myeloma peripheral blood B cells to bone marrow fibroblasts: a requirement for CD44 and alpha4beta7." CANCER RESEARCH, (1997 MAR 1) 57 (5) 930-6. , XP002132841 abstract page 930, right-hand column, line 11-36 page 935, right-hand column, paragraphs 3,4 figure 2 <div style="text-align: center;"> --- -/-- </div>
Relevant to claim No. <div style="text-align: center;">1-5,7-9</div>	
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>	
* Special categories of cited documents : <div style="display: flex;"> <div style="flex: 1;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>	
Date of the actual completion of the international search <div style="text-align: center;">13 March 2000</div>	Date of mailing of the international search report <div style="text-align: center;">28/03/2000</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <div style="text-align: center;">Covone, M</div>

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International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US ROODMAN G D: "Mechanisms of bone lesions in multiple myeloma and lymphoma." retrieved from STN Database accession no. 1998026745 XP002132842 abstract & CANCER, (1997 OCT 15) 80 (8 SUPPL) 1557-63. REF: 39 ,</p>	<p>1-3, 10-12, 20-22</p>
X	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, USAugust 1998 (1998-08) AKATSU TAKUHIKO ET AL: "Chinese hamster ovary cells expressing alpha4beta1 integrin stimulate osteoclast formation in vitro." Database accession no. PREV199800429141 XP002132843 abstract & JOURNAL OF BONE AND MINERAL RESEARCH AUG., 1998, vol. 13, no. 8, August 1998 (1998-08), pages 1251-1259, ISSN: 0884-0431</p>	<p>1-3, 10-12, 20-22</p>
A	<p>US 5 510 332 A (KOGAN TIMOTHY P ET AL) 23 April 1996 (1996-04-23) column 2, line 3-12 claims</p>	<p>1-29</p>
A	<p>DATABASE SCISEARCH 'Online! MICHIGAMI T (REPRINT) ET AL: "Interactions of myeloma cells with bone marrow stromal cells via alpha 4 beta 1 integrin - VCAM - 1 is required for the development of osteolysis." retrieved from STN Database accession no. 684996 XP002132844 abstract & JOURNAL OF BONE AND MINERAL RESEARCH, (AUG 1997) VOL. 12, SUPP. '1', PP. 104-104. PUBLISHER: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148. ISSN: 0884-0431., UNIV TEXAS, HLTH SCI CTR, SAN ANTONIO, TX 78284</p>	<p>1-29</p>

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/21170

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 61421 A (GILL ALAN ;BIOGEN INC (US); LEE WEN CHERNG (US)) 2 December 1999 (1999-12-02) page 3, line 27 -page 4, line 1 page 9, line 1 -page 11, line 15 claim 1	1-3,8,9
T	MORI Y (REPRINT) ET AL: "Anti- alpha 4 integrin antibody suppresses the bone disease of myeloma and disrupts myeloma -marrow stromal cell interactions." JOURNAL OF BONE AND MINERAL RESEARCH, (SEP 1999) VOL. 14, SUPP. '1', PP. 1161-1161. PUBLISHER: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148. ISSN: 0884-0431., XP000877429 UNIV TEXAS, HLTH SCI CTR, SAN ANTONIO, TX;BIOGEN, CAMBRIDGE, MA the whole document	1-29

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/21170

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/21170

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5510332	A	23-04-1996	NONE	
WO 9961421	A	02-12-1999	NONE	